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Risk of myocardial infarction after oophorectomy and hysterectomy

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Abstract

To determine the risk of developing a first myocardial infarction after a hysterectomy and/or oophorectomy. Case-cohort analysis performed among 17,126 women in the Uppsala Health Care Region of Sweden, who had undergone a hysterectomy and/or oophorectomy in 1965 to 1983. Record linkage was used for follow-up and medical records to ascertain the actual history of oophorectomy. Risk estimates were calculated by relating the observed number of cases in the cohort to that expected on the basis of incidence rates in the population. Overall, 214 cases of myocardial infarction were observed. In premenopausal women a bilateral oophorectomy alone tended to increase the relative risk 1.6; 95% CI 0.8–3.1, but this operation combined with hysterectomy increased the risk only among those aged 50 and over at surgery. Hysterectomy at premenopausal age or unilateral oophorectomy did not alter the risk of myocardial infarction. In naturally menopausal women, hysterectomy—mainly for uterine myoma—was associated with a four-fold increase in relative risk (3.8; 95% CI 1.9–7.8). Hysterectomy for treatment of myoma performed after a natural menopause is linked to an excess risk for myocardial infarction. Bilateral oophorectomy before menopause may increase the risk of myocardial infarction.

Keywords: Hysterectomy; Oophorectomy; Acute myocardial infarction; Case cohort study; Natural menopause; Myoma

1. Introduction

Estrogen deficiency at the time of natural menopause may promote atherosclerotic disease. It is not clear, however, which is the most important as risk factor for cardiovascular disease: the postmenopausal status compared with the premenopausal, to have an early menopause, or to have a "surgical menopause" [1–10]. A bilateral oophorectomy at a premenopausal age results in a sudden and substantial drop in the serum level of estrogen, which could accelerate atherosclerosis [10] and development of coronary heart disease.

Further, removal of one ovary or the uterus could increase the risk of developing coronary heart disease [1–5, 8–9,11] by reducing the estrogen level or being associated with other endocrine changes [9,11]. Alternatively, conditions leading to surgery may involve a hormonal imbalance [12] or exposure to treatments that affect the risk of myocardial infarction. Even in a naturally menopausal woman a hysterectomy or oophorectomy may induce hormonal changes or reflect an adverse hormonal background.

The aim of our study was to investigate whether a unilateral or bilateral oophorectomy, or a hysterectomy, increases the risk of myocardial infarction. A large population-based cohort of Swedish women who had undergone a hysterectomy and/or oophorectomy was followed up through record linkage to ascertain hospital admissions for a first instance of myocardial infarction. As reference we used all women in the background population living in the same geographic region.

2. Material and methods

Women living in the Uppsala Health Care Region of Sweden (six counties in the central part of Sweden, with about 1.48 million inhabitants in 1983) who had undergone a hysterectomy and/or oophorectomy between 1965 and 1983 were identified from an Inpatient Registry, which includes data on all patients admitted to hospitals for somatic care. The registry data include a National Registration Number (a 10-digit number which permits exclusive identification of the individual and linkages between registries), the date of admission, and numerical codes for diagnoses (indications for the operation) and surgical procedures. Coverage of admissions is known to be 97% complete [13].

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A total of 22,121 women were registered as having had a hysterectomy and/or oophorectomy. Women in whom the indication for surgery was cancer (except cancer in situ of the cervix) were excluded ($n = 4,456$), as were those in whom a malignancy had been diagnosed within 90 days of surgery ($n = 232$) and those who had emigrated ($n = 43$). Furthermore, we omitted women who had had any of the procedures on more than one occasion ($n = 238$), and women who had had a myocardial infarction before surgery ($n = 26$). Thus, 17,126 women constituted the cohort at risk of suffering a first myocardial infarction.

All women admitted to hospital with a first acute myocardial infarction were identified through record linkage within the Inpatient Registry. An acute myocardial infarction was defined by the *International Classification of Diseases* (ICD) codes, 420.10 and 420.17 (7th revision) during 1965-1968, and 410.00 and 410.99 (8th revision) during 1969-1983. In all, 214 cases were found in the cohort.

As full information on the ovarian status after the surgery in all cohort women was not included in the Registry, we collected information on the surgical procedures in all cases of myocardial infarction and in a randomly chosen subcohort by examining medical records. The size of the subcohort, $n = 1,339$, was approximately six times the number of myocardial infarctions. The medical records were examined by three of us without knowledge of the case status of the woman, abstracting on a standard form: (1) type of menopause, i.e., natural or "surgical" due to hysterectomy and/or bilateral oophorectomy; (2) age at menopause; (3) surgical procedure (unknown type of operation for those with missing medical record); (4) indications for the operation. Menopause was defined as natural if menstruation had ceased more than 6 months prior to the operation.

Records were also scrutinized for pertinent myocardial infarction risk factors, with sufficiently complete information only regarding hypertension and diabetes. Information on hormone replacement therapy was too sparse to be used in the main analyses. The medical records were found for 207 of the case women (97%) and 1,307 of the randomly selected subcohort (98%).

2.1. Statistical methods

Main analyses are based on the case cohort methodology, i.e., exposure experience of the randomly selected subcohort (expressed as its person-years) represented the entire cohort [14], and Dr. Jay Lubin, NCI, personal communication. The number of person-years was calculated from the date of the operation until the end of follow-up (December 31, 1983) or the date of death, emigration, or admission for a myocardial infarction, whichever occurred first. Dates of deaths were ascertained from the Causes of Death Registry. The expected number of cases was obtained from person-year counts and female population incidence rates of myocardial infarction from the same region in the Inpatient Registry. The incidence rates were calculated from the annual numbers of first myocardial infarctions, in all 16,455 cases, and the mid-year population by five-year age groups. No adjustment of the incidence rates in the underlying population was made, as the number of person-years (pyr) in the cohort accounted for only 1.4 percent of that in the background population. As the subcohort constituted 11,860.40 person-years, i.e., 7.82% of the final cohort, the expected values derived from the subcohort were divided by 0.0782 to obtain an estimate of the expected values for the entire cohort.

Standardized incidence ratios, denoted here as relative risk (RR), were calculated by dividing the observed number of cases by the number expected. The observed cases were assumed to have a Poisson distribution.

Data obtained from the medical records of the subcohort women were used to estimate the proportion of women in the final cohort whose operation occurred premenopausally or resulted in cessation of menstruation, and the proportion whose operation occurred after a natural menopause. If the menopausal status was not mentioned in the medical record but the operation occurred before the age of 46, the woman was classified as premenopausal at the time of the operation (one case of myocardial infarction). If the woman was over the age of 54 at operation and without menstrual periods, or a prior operation leading to menopause or a radiation-induced menopause was not mentioned, this woman was considered to have had a natural menopause (8 cases).

The relative risk including 95% confidence intervals (CI) was estimated by a piece-wise exponential regression model in which the variability in the observed numbers of cases and the added variability in the expected values due to the sampling of the cohort was considered (14). No external adjustments could be made because of a lack of risk factor data in the background population. For confounding variables such as diabetes and hypertension, Poisson regression models *within* the subcohort were used.

3. Results

The total number of person-years by the end of 1983 was 151,620 and the average observation time 8.9 years. The average age of the cohort women when admitted for operation was 45.9 years. Approximately 72% of the women were operated on before the age of 50 representing 76% of the person-years. The distribution of person-years by age in the subcohort was nearly identical to that in the cohort.

The observed number of cases of myocardial infarction in the total cohort was 214, compared with an expected number of 213.7 based on person-years for the entire cohort, yielding a relative risk estimate of 1.00 (95% CI 0.87–1.14), with the case-cohort approach a similar risk estimate of 1.03 (95% CI 0.89–1.19) was found.

Subjects in the subcohort whose type of operation was other surgery only or unknown (8 cases and 400.1 person-years, or 3.4% of the whole subcohort, respectively), were excluded from further analyses, as were 7 cases (737.2 pyr

or 6.2%) in women with unknown menopausal status at operation. Subjects premenopausal at the time of surgery contributed 88 cases and 76% of the person-years and those naturally menopausal contributed 111 cases and 14% of the person-years to the analyses according to menopausal status.

In premenopausal women, analyses by type of surgery showed no significant deviations of the relative risks from unity; the risk estimate for bilateral oophorectomy alone was 1.6 (95% CI 0.8–3.1). All premenopausal women with both ovaries removed by the operation had a relative risk of 1.2 (95% CI 0.8–1.7) (Table 1).

Naturally menopausal women with bilateral oophorectomy alone had no increased risk, while bilateral oophorectomy combined with hysterectomy was associated with a relative risk of 1.4 (95% CI 1.0–2.0) (Table 1). Women with a unilateral oophorectomy alone had a possibly reduced risk estimate, 0.5 (95% CI 0.3–1.0). Hysterectomy alone as well as hysterectomy combined with unilateral oophorectomy conferred an almost four-fold excess risk (RR = 3.8); these two latter groups together had a relative risk estimate for hysterectomy *with or without* unilateral oophorectomy of 3.8 (95% CI 1.9–7.8).

With regard to age at operation among premenopausal women the highest risk estimate was found for those aged 45 to 49 years at time of bilateral oophorectomy alone, (RR = 1.9), however this estimate had a wide confidence interval (95% CI 0.7–4.8) (Table 2). No increase in the relative risk was noted for bilateral oophorectomy, irrespective of hysterectomy before age 49, but when performed at older ages the relative risk was elevated to 1.6 (95% CI 1.0–2.5). No association with age at unilateral oophorectomy alone, or at hysterectomy alone or combined with unilateral oophorectomy emerged.

Analyses by years since a premenopausal operation (Table 3) showed a tendency towards elevated risk in women with a premenopausal bilateral oophorectomy at ages 50 years or older regardless of follow-up length. Naturally menopausal women with bilateral oophorectomies had no change in risk by years since the operation, RR = 1.0 vs. 1.2 (data not in table). The postmenopausally hysterectomized women had a roughly five-fold significant increase in risk 5+ years following surgery, RR = 4.5; 95% CI 1.9–11, the relative risk within five years of surgery was lower (2.8; 95% CI 0.8–9.4).

The predominant indication for hysterectomy was clearly the presence of uterine myoma (listed in 75% of all the medical records), with small percentages for abnormal bleeding (19%), endometriosis (11%), or other reasons (22%) (Table 4). The relative risk of myocardial infarction after hysterectomy performed for myoma was not increased when we analyzed the women together, but it was significantly increased after this operation in naturally menopausal women (RR = 6.2; 95% CI 1.9–20). The risk associated with premenopausal hysterectomy performed for bleeding and "other" reasons seemed to be elevated (2.0; 95% CI 0.8–4.9 and 1.4; 95% CI 0.7–3.1, respectively). In naturally menopausal women the risk associated with "other" reasons was 3.1; 95% CI 0.9–11. In most instances, the results were similar when the analyses were limited to operations performed on one indication only (shown for all women in Table 4). However, in naturally menopausal women the risk associated with myoma only tended to be higher (RR = 7.6; 95% CI 1.8–32) as compared with myoma in the presence of other indications.

Analyses of indications for oophorectomy alone for women with a bilateral oophorectomy at age 50 or later or unilateral oophorectomy showed that in 55% a benign ovarian neoplasm was noted as an indication for the operation, whereas cysts and endometriosis were noted in 21% and 13% of the medical records, respectively (Table 4). In premenopausal women, ovarian neoplasm as an indication for operation appeared to increase the risk, especially as the only indication (RR = 2.0; 95% CI 0.9–4.3).

Information on hormone replacement was found in the medical records in only about 60% of the women with a bilateral oophorectomy, and in 40% of the women in other op-

Table 1
Observed and expected numbers of cases of acute myocardial infarction associated with selected gynecological operations,[a] with relative risk estimates (RR),[b] and 95% confidence intervals (CI)

	Premenopausal at time of operation[c]			Naturally menopausal at time of operation		
Operation	Observed	Expected	RR (95% CI)	Observed	Expected	RR (95% CI)
Bilateral oophorectomy	34	29.0	1.2 (0.8–1.7)	90	80.6	1.1 (0.9–1.4)
Alone	9	5.8	1.6 (0.8–3.1)	47	50.1	0.9 (0.7–1.3)
With hysterectomy	25	23.2	1.1 (0.7–1.6)	43	30.5	1.4 (1.0–2.0)
Unilateral oophorectomy	26	26.5	1.0 (0.7–1.5)	Not done		
Alone	8	8.7	0.9 (0.5–1.9)	11	21.8	0.5 (0.3–1.0)
With hysterectomy	18	17.8	1.0 (0.6–1.6)	3	0.8	3.8 (1.1–13.4)
Hysterectomy[d]	46	43.7	1.1 (0.8–1.4)	10	2.6	3.8 (1.9–7.8)
Alone	28	25.9	1.1 (0.7–1.6)	7	1.8	3.8 (1.6–9.1)
Overall	88	81.4	1.1 (0.9–1.3)	111	105.0	1.1 (0.9–1.3)

[a] Those with other or unknown types of operation or an uncertain menopausal status are not included.
[b] Derived from case-cohort analyses.
[c] Operation resulted in cessation of menstruation, except in those who underwent a unilateral oophorectomy alone.
[d] Excludes those who also had a bilateral oophorectomy; includes those who also had a unilateral oophorectomy.

Table 2
Relative risk estimates (RR) of acute myocardial infarction, with 95% confidence intervals (CI),[a] associated with age at gynecological operations, among women who were premenopausal at the time of surgery; the numbers of observed and expected cases are given

Operation	Age (years)	No of observed	No of expected	RR (95% CI)[b]
Bilateral oophorectomy alone	<45	1	1.1	0.9 (0.0–28)
	45–49	5	2.6	1.9 (0.7–4.8)
	⩾50	3	2.1	1.5 (0.4–5.0)
Bilateral with hysterectomy	<45	1	1.5	0.7 (0.1–5.0)
	45–49	6	10.8	0.6 (0.2–1.3)
	⩾50	18	11.0	1.6 (1.0–2.7)
Combination of all bilateral oophorectomy	<45	2	2.6	0.8 (0.2–3.2)
	45–49	11	13.4	0.8 (0.4–1.5)
	⩾50	21	13.1	1.6 (1.0–2.5)
Unilateral oophorectomy alone	<45	6	5.6	1.1 (0.5–2.4)
	45–49	2	1.5	1.3 (0.3–5.4)
	⩾50	—	1.5	—
Hysterectomy[c]	<45	15	15.3	1.0 (0.6–1.6)
	45–49	23	19.9	1.2 (0.8–1.8)
	⩾50	8	8.5	0.9 (0.5–1.9)

[a] Derived from case-cohort analyses.
[b] Tested for trend with Spearman's rank correlation coefficient.
[c] Excludes those who also had a bilateral oophorectomy; includes those who also had a unilateral oophorectomy.

eration categories. The relative risk in the estrogen users who underwent any type of surgery before the age of 50 years was 0.6 (95% CI 0.3–1.1) compared with 1.1 (95% CI 0.8–1.4) for nonusers and unknown use. For history of diabetes and hypertension, adjustments in analyses showed no effect on the risk estimates (data not given).

4. Comment

Our finding of an increased risk of myocardial infarction associated with surgical treatment of uterine myomas in menopausal women is intriguing. The bleedings accompanying the myomas perimenopausally are often dysfunctional, and commonly treated pharmacologically with high dosages of progestins administered cyclically [15]. Such treatment may have been particularly protracted in these women who developed or were left with symptoms postmenopausally [12,16]. The progestin treatment could entail an increased risk of myocardial infarction mainly through an adverse effect on lipoprotein patterns [17]. However, there might also be a specific endocrinological disturbance underlying both the development of myomas and increased atherosclerosis leading to myocardial infarction. The natural history and pathogenesis of myomas is still unclear. Women with uterine myoma tend to have a higher education, higher body mass index and are less frequent smokers [18,19]. There are few data in the literature to support a link between uterine myoma and the risk of myocardial infarction [11], and the conditions leading to hysterectomies have not been considered in previous studies.

In the study we could not confirm earlier findings of an elevated risk in women undergoing premenopausal bilateral oophorectomy, although the risk for myocardial infarction may be increased in premenopausal women who have both ovaries removed while retaining the uterus.

The strength of our study includes the population based cohort design with a virtually complete follow-up, an efficient case-cohort approach, and an unbiased ascertainment of the exposure status directly from the medical records. A weakness, as in other studies, was the small number of myocardial infarction cases in premenopausal women, which limited the power of the subgroup analyses.

Our results may be biased if the age distribution at natural menopause differs between women in the reference population—from which incidence rates were determined—and the cohort women. Nearly all women under the age of 40, approximately 80–90% of women aged 40–44, but only half of the women at the age of 50 would be expected to be premenopausal (6), which means that the expected estimates reflect a risk in premenopausal women only among the youngest. If a natural menopause increases the risk of myocardial infarction [3,5], our results will be biased towards unity with increasing age, i.e., we will underestimate a possible relationship with oophorectomy in premenopausal women. However, for women under 45 years of age at operation, and during the initial years after operation, this bias will be small.

Women who had gynecological cancer as a reason for the operation were excluded from the cohort which may have introduced a bias due to healthy subject selection in re-

Table 3
Relative risk estimates (RR) and 95% confidence intervals (CI)[a] for acute myocardial infarction by type of operation, age at operation, and years since operation among women who were premenopausal at the time of surgery; Observed (O) and expected (E) numbers of cases are given

		Years since operation					
		0–5 years			5 years and more		
Operation	Age at operation	O	E	RR (95% CI)	O	E	RR (95% CI)
Bilateral oophorectomy with or without hysterectomy	<50 years	2	3.0	0.7 (0.2–2.7)	11	12.9	0.9 (0.5–1.6)
	⩾50 years	7	3.8	1.9 (0.6–5.6)	14	9.3	1.5 (0.9–2.6)
Unilateral oophorectomy alone		2	1.5	1.3 (0–52)	6	7.2	0.8 (0.4–1.9)
Hysterectomy alone or with oophorectomy		7	8.7	0.8 (0.4–1.7)	39	35.1	1.1 (0.8–1.5)

[a] Derived from case-cohort analyses.

Table 4
Relative risk estimates (RR) and 95% confidence intervals (CI)[a] for acute myocardial infarction by indications for operation; observed (O) and expected (E) numbers of cases are given

All women, independent of menopausal status							
	Primary indications				"Only" indications		
	O	E	RR (95% CI)		O	E	RR (95% CI)
Indications in those who underwent a hysterectomy without ovarian ablation							
Myoma[b]	27	25.1	1.1 (0.7–1.6)	Myoma only	21	19.1	1.1 (0.7–1.7)
Bleeding[b]	5	2.8	1.8 (0.7–4.3)	Bleeding only	1	1.8	0.6 (0.1–4.1)
Endometriosis[b]	1	1.7	0.6 (0.1–4.2)	Endometriosis only	—	0.3	—
Other reasons[b]	10	6.2	1.6 (0.8–3.1)	Other reasons only	5	2.5	2.0 (0.8–5.1)
Indications in those who underwent an oophorectomy without a hysterectomy[c]							
Ovarian neoplasm[b]	55	59.1	0.9 (0.7–1.2)	Ovarian neoplasm only	46	46.7	1.0 (0.7–1.4)
Ovarian cyst[b]	6	11.3	0.5 (0.2–1.3)	Ovarian cyst only	4	8.6	0.5 (0.2–1.4)
Endometriosis[b]	2	2.0	1.0 (0.2–4.5)	Endometriosis only	2	0.4	5.0 (1.2–21)
Other reasons[b]	13	21.4	0.6 (0.3–1.1)	Other reasons only	6	10.6	0.6 (0.2–1.3)

[a] Derived from case-cohort analyses.
[b] May also have had other indications.
[c] Among women who underwent a unilateral oophorectomy without hysterctomy at any age or a bilateral oophorectomy without a hysterectomy at age 50 years or older.

lation to the reference population, and imply an underestimation of the risk of myocardial infarction. To include them might have introduced an overrisk depending both on the cancer itself and the often harsh curative treatment [20]. However, women with malignancies constituted only a small proportion of the study base in the age groups under 50 years.

Crucial to the interpretation is the possibility of confounding by other risk factors. Diabetes mellitus, hypertension, and smoking are strong risk factors for myocardial infarction [21]. However, risk factor data from the reference population were not available for direct calculation of adjusted estimates. Data on a history of diabetes mellitus or hypertension, abstracted when available from medical records for cases and the subcohort, were used for adjustment in internal comparisons of the different operation categories. These analyses did not produce any substantial changes in the risk estimates. Absence of an increased risk could, however, be due to a lower baseline risk in the operation cohort compared with the reference population on account of differences in these two or other risk factors.

Observational studies have found a protective effect of hormone replacement on the risk of coronary heart disease [22,23]. Use of estrogens after the operation might weaken a possible negative effect of a gynecological operation on the risk of myocardial infarction. As women who have undergone a bilateral oophorectomy or a hysterectomy more often have climacteric symptoms [24,25] these women might be more likely to take replacement hormones than the general population. Using the available, crude and probably incomplete information on estrogen replacement after operation, an analysis showed a beneficial effect of estrogen on the risk of myocardial infarction in the whole subcohort regardless of type of operation. Thus, the magnitude of the adverse effect of oophorectomy or hysterectomy may have been underestimated in our study.

Several studies have reported of a two fold increased risk of coronary heart disease [1–5] and atherosclerosis [10] after a premenopausal bilateral oophorectomy, an increased risk with decreasing age at operation, and persistence of the risk elevation after 10 years [2]. However, estrogen replacement therapy eliminates this adverse effect [3]. We found an insignificantly increased risk for myocardial infarction in women undergoing a bilateral oophorectomy alone at a young age, but not when accompanied by a hysterectomy. However, we could not evaluate the possible effect of estrogen replacement. It is notable that the risk after a bilateral oophorectomy combined with hysterectomy tended to be elevated in both premenopausal women ages 50 years or older and in women who were postmenopausal at surgery.

As regards premenopausal hysterectomy, with retention of at least one ovary, an increased risk of coronary heart disease has been suggested [1,2,4,8], though not in all studies [3,6,11]. We found no excess risk after a premenopausal hysterectomy or after removal of one ovary, but an increased risk of myocardial infarction after a postmenopausal hysterectomy alone or together with removal of one ovary, an association perhaps explained by the underlying condition, i.e., uterine myoma. To our knowledge, no previous study has examined the risk of coronary heart disease after hysterectomy in women after a natural menopause.

In summary, our findings indicate there may be an adverse effect of premenopausal, ovarian ablation on the risk of myocardial infarction. Further, a premenopausal hysterectomy or removal of one ovary may not substantially alter risk, while hysterectomy performed for uterine myoma after a natural menopause is linked to an excess risk of coronary heart disease. Tentatively, this could be explained by endocrinological characteristics underlying the development of myomas or by adverse effects of progestin treatment, rather than a direct effect of the operation itself.

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